Systemic Lupus Erythematosus

FOR OVER HALF A CENTURY systemic lupus erythematosus (SLE) was considered a rare and fatal disease. During the 1930s suspicions arose that hypersensitivity might be involved in pathogenesis. In 1948 the LE cell was discovered. In the 1950s the application of immunological techniques in the study of SLE led to the identification of autoimmunity in man, and established that the formation of LE cells is an immunological event. In succeeding years the use of diagnostic immunological techniques has led to the recognition of an extraordinarily broad spectrum of clinical forms of SLE affecting many different major organ systems with intensities from mild to fulminating.

During the same period, the discipline of immunology has rapidly matured. Transplantation immunology has emerged, and with it a recognition of the phenomenon of immunological tolerance which is a state of unresponsiveness to antigen antithetical to classical sensitivity. The cellular events which constitute the immune response have at least in part been identified and thereby the sequential components of that response have been opened for study. Much of the molecular structure of antibody is now known. The role of individual genotype in governing the immune response is being established. Autoimmunity has become a recognized component of diseases in fields as previously separate as Rheumatology, Endocrinology, Gastroenterology, and Neurology.

Matters have progressed further. It is now well established that autoantibodies to a tissue can in certain instances protect that tissue from immunologically induced disease. Certain types of viral infections are apparently harmless until host defenses come into play; then the cellular protection responses damage host tissue and produce disease. These two phenomena suggest that what would be expected to be harmful may be helpful in certain circumstances, and vice versa. Furthermore, states of immunological sensitivity and tolerance can coexist in the same animal, with first one and then the other predominating. The immune response of the whole animal is malleable. The implications of this flexibility as it affects the intensity, quality, and reversibility of immune responses are only beginning to be understood.

The conference from UCLA on Systemic Lupus Erythematosus, published in this issue, illustrates many recent advances and underscores many current problems in clinical immunology. It is now possible to identify multiple variations of the classical clinical categories of rheumatic disease and to observe one evolve into another. It is also possible to identify specific immunological events accompanying certain types of disease, such as the association of autoantibody to DNA with nephritis. The converse association, involving the protective effect of certain autoantibodies, has also been established in experimental disease and suggested in SLE. In experimental animals, analogues of autoimmune hemolytic anemia and SLE arise naturally in strains with particular genotypes as a product of aging or possibly viral infection.

We still do not understand, however, the associations of particular serological abnormalities with patterns of clinical disease, the variations in serological patterns which accompany transformation of one clinical form into another, or even the natural history of most variants of SLE. We have only very modest knowledge of the mechanisms of tissue damage. It remains very difficult to establish an appropriate prognosis for individual patients or to decide with accuracy the type and intensity of treatment which is needed.

The current treatment of immunological diseases further emphasizes our ignorance. Corticosteroids have enjoyed widespread use in the treatment of these diseases since the early 1950s. Experience establishes beyond doubt that they can terminate the lupus crisis. However, there still does not exist a single controlled study demonstrating conclusively the benefit of these agents. Their comparative utility in different forms of SLE and related diseases is also unresolved. Recently it has become popular to use cytotoxic agents, particularly in the treatment of patients who appear resistant to corticosteroids. The rational is sound: Cytotoxic agents

inhibit the primary immune response, reduce the secondary response, interfere with cellular hypersensitivity, diminish inflammatory reactions, facilitate the induction of immunological tolerance in certain settings and impede the development of experimental immunological disease. However, the clinical literature on the use of these agents contains only reports of treatment of small numbers of patients and uncontrolled evaluations. Some clinical evidence has been presented suggesting that a combination of corticosteroids and cytotoxic agents is superior to either type of agent alone, but here too the data are not rigorous. Preliminary controlled investigations suggest that the cytotoxic drugs alone are often ineffective in influencing immunological disease. Furthermore the price paid by patients receiving combined therapy is very high in terms of opportunistic infections which have become a frequent cause of serious morbidity and death.

The discussion from UCLA serves to emphasize the needs for the next few years. These include careful clinical observations (1) to establish the natural history of various forms of SLE, (2) to identify rigorously the patterns and significance of different serological reactions in relation to pathogenesis, prognosis and response to therapy and (3) to determine the efficacy of various treatment programs. The influence of patient genotype and of viral infection on susceptibility to immunological disease requires definition. Study of mechanisms of tissue damage may be difficult in man but animal models now provide appropriate subjects for investigation. It should be possible, once these mechanisms are identified, to design specific therapeutic programs to counteract them. The flexibility and adaptability in the immune response make such therapeutic manipulations more than a distant hope; if autoimmunity results from a loss of natural tolerance, perhaps we can discover biological ways to reestablish that tolerance.

The conceptual and methodological tools are at hand to accomplish these objectives. In the past, the study of human disease has provided a great portion of the impetus for the growth of the discipline of immunology. We may hope that more rigorous study of human disease will now yield both improved care of patients and an even greater increment in knowledge of the human immune response.

HALSTED R. HOLMAN, M.D.
Stanford University School of Medicine

Polymyalgia Rheumatica

AMERICAN PHYSICIANS have been slower than those in Britain to accept polymyalgia rheumatica as a distinct clinical syndrome. Perhaps it is less common in North America than in Europe. Nevertheless, once a case is recognized others seem to appear and the incidence may not differ greatly on the two sides of the Atlantic Ocean. In any event, the incidence if it be different has not attracted the attention of epidemiologists.

A more immediate problem, because it has important clinical implications, is the relationship of polymyalgia rheumatica to the syndrome of giant cell arteritis. That name is slowly gaining favor over the terms *temporal* or *cranial* arteritis because it is clear that on occasion the disease can affect any part of the aorta or its branches.

There is general agreement that the musculoskeletal symptomatology of polymyalgia rheumatica and giant cell arteritis is the same and that patients ultimately proven to have giant cell arteritis may have a prodrome of polymyalgia for several years before arterial changes become evident.[1] Unfortunately, it has been well documented that blindness or a serious cerebrovascular accident may be the first manifestation of the arteritis.[2]

Both polymyalgia rheumatica and giant cell arteritis are dramatically improved by corticosteroid therapy. So striking is the response of the former, even to small doses, that the therapeutic effect has been proposed as a diagnostic test. Larger amounts, however, may be required to control the manifestations of giant cell arteritis, and the frequency of complications, especially osteoporosis in the elderly population characteristically affected, becomes a major concern.

Both diseases tend to have self-limited courses extending over a few months to a year or two, but relapses may occur[3] and there is no established means of knowing when therapy can be stopped. The author knows of three patients with temporal